REMARKS

Preliminary Amendments to the Claims

Pursuant to 37 CFR 1.115, Applicants have preliminarily amended Claims 1-5, 8-12, 19, and 25, and added new Claims 32-39, as indicated in the Listing of the Claims (above) and as explained below.

Claim 1, which covers a method of treating obesity in a vertebrate animal, has been amended to make clear that the method comprises administering to the animal a compound that is a trichothecene or a derivative thereof and that the compound has the critical property of stimulating a fed pattern of gut motility in the animal. Applicants also amended Claims 2-5, which depend from Claim 1, to incorporate the term "compound" and thereby maintain consistent use of terms throughout the claims. Support for the amendments is found in the specification (see, e.g., p. 11, line 30-p. 12, line 5; p. 15, lines 20-22; Example 1, p. 31, line 23-p. 41, line 10, of the specification). Accordingly, the amendments add no new matter.

Applicants have similarly amended independent Claim 8, which covers a method of stimulating fed pattern of gut motility in a vertebrate animal, to make clear that the method comprises administering to the animal a compound that is selected from a group of several classes of compounds described in the specification. Applicants also amended Claims 9-12, which depend from Claim 8, to incorporate the term "compound" and thereby maintain consistent use of terms throughout the claims and, where appropriate, to eliminate recitation of unnecessary terms. Support for the amendments is found in the specification (see, e.g., p. 4, lines 1-23; p. 15, lines 18-31, of the specification).

Claims 2 and 9, which depend from Claims 1 and 8, respectively, have also been amended to cover the embodiments wherein the compound is a trichothecene or derivative thereof selected from a particularly preferred group of compounds. Applicants have also amended Claim 10 to depend from Claim 9 (instead of Claim 8) to expressly cover a method of treating obesity using a particular species (i.e., DON) from the preferred compounds listed in Claim 9. Support for the amendments is found in the specification (see, e.g., p. 3, lines 13-32; p. 20, line 11-p. 21, line 32, of the specification). Accordingly, the amendments add no new matter.

Applicants have amended Claim 25 to direct coverage to a pharmaceutical composition of the invention comprising a compound selected from the same group of preferred compounds mentioned in amended Claims 2 and 8. Support for the amendment is found in the specification (see, e.g., p. 21, lines 11-32, of the specification). Accordingly, the amendment adds no new matter.

Finally, Applicants have added new Claims 32-39 to expressly cover methods of the invention for regulating food intake by a vertebrate animal comprising administering to the animal a compound that is selected from a group of several classes of compounds described in the specification and having the critical property of stimulating a fed pattern of gut motility in the animal. Support for new Claims 32-39 is found throughout the specification (see, e.g., p. 11, line 2-p. 12, line 9; p. 15, line 18-p. 16, line 2; p. 20, line 11-p. 24, line 23, of the specification). Accordingly, new Claims 32-39 add no new matter.

Entry of the amendments and new Claims 32-39 presented in the Listing of the Claims, above, is respectfully requested under 37 CFR 1.115.

Unity of Invention Under PCT Rule1 13.1-13.2

In the Office Action (Paper No. 7), the Examiner viewed the claims as lacking unity of invention and, therefore, divided Claims 1-31 into six groups (Groups I-VI) as follows:

Group I:	Claims 1-7, drawn to a method of treating obesity
Group II:	Claims 8-15, drawn to a method of stimulating a pattern of gastric [sic] motility
Group III:	Claims 16-18, drawn to a method of increasing weight
Group IV:	Claims 19-21, drawn to a method of preventing gut motility [sic]
Group V:	Claims 22-24, drawn to a method of identifying a compound
Group VI:	Claims 25-31, drawn to a pharmaceutical composition

Although the Examiner's statement following each grouping of the claims in the Office Action is understood to be, at best, a brief description of the subject matter of the claims, Applicants note for clarity that with respect to Group II, Claims 8-15 cover "a method of stimulating ***fed pattern of gut motility***", i.e., the claims do not recite and are not limited to "a method of stimulating a pattern of gastric motility". With respect to Group IV, Claims 19-21 cover "a method of preventing ***fed pattern*** of gut motility", ***not*** "a method of preventing gut motility". With respect to Group V, Claims 22-24 cover "a method of identifying a compound for treating obesity comprising determining whether the compound ***is capable of inducing fed pattern gut motor activity***".

In the Office Action, the Examiner asserts that the above subdivision and groupings of the claims are necessary because the claims do not relate to a single general inventive concept under PCT Rule 13.1 and that the claims lack the same or corresponding special technical feature required by PCT Rule 13.2. Applicants respectfully traverse the Examiner's view and provide a brief review of the invention below to show that the claims are, in fact, so linked as to form a single general inventive concept consistent with PCT Rule 13.1 and possess common special technical features that effectively unify the claims as required by PCT Rule 13.2.

Applicants' invention provides methods and compositions comprising a compound that has the technical feature of possessing the ability to regulate the pattern of gut motor activity ("gut motility") that is associated with the regulation of food intake by vertebrate animals. A compound useful in the compositions and methods of the invention may be a trichothecene compound, a derivative of a trichothecene, or another compound described in the specification that has the ability to regulate gut motility.

This invention is based on Applicants' initial discovery that trichothecenes and derivatives thereof are able to regulate gut motility associated with food intake in vertebrate animals. A variety of trichothecenes are known to be produced by fungi, such as species of *Fusarium*, which may contaminate food, especially cereals and other crops, used for livestock feed and for human consumption. For decades, the ingestion of trichothecenes such as 4-deoxynivalenol ("DON", also referred to as "vomitoxin") present on fungally contaminated food has been assumed to be responsible for any of a number of "toxic symptoms", including emesis (vomiting), feed refusal by livestock, loss of weight or lack of weight gain in livestock, skin irritation, diarrhea, leukopenia, hemorrhage, necrotic angina, marrow depletion, respiratory

failure, and even death (see, e.g., Ueno, *Adv. Nutrit. Res., 3*: 301-353 (1980), of record). Hence, the literature on trichothecenes has focused on the toxicology or the chemistry of trichothecene compounds as fungal toxins ("mycotoxins"). Practical concerns over loss of economic benefit in marketable livestock and potential harm to human populations have provided the primary impetus for such studies (see, e.g., Arnold et al., *Fund. Appl. Toxicol., 6*: 691-696 (1986), of record). Accordingly, such compounds have been universally viewed as toxic compounds that lack any useful pharmacological or physiological activity.

Contrary to the prevailing assumptions and teachings of the mycotoxin literature, Applicants discovered that a variety of purified trichothecenes and derivative compounds surprisingly exhibit a pharmacological activity that is likely to have an enormous therapeutic and/or prophylactic benefit to the health of humans and other animals. In particular, Applicants found that such trichothecenes and derivative compounds described in the specification act non-toxically and outside of the gut tissues and organs as neuroregulatory agents of a specific neural pathway comprising the enteric P_{2X1} purine receptor (i.e., the P_{2X1} purinoceptor found innervating gut tissues and organs) to modulate ***the pattern*** of gut motor activity (or "gut motility"), i.e., the pattern of contractions and relaxations in the gut tissues and organs, and to do so in a manner that is comparable to the normal gut motor activity that occurs after an individual ingests food (see, e.g., the specification at p. 11, line 30-p. 12, line 9; p. 15, lines 18-26; Examples 3-5, p. 46, line 1-p. 60, line 29). Thus, stimulation of "fed pattern" gut motor activity signals satiety, i.e., the feeling of fullness, which prompts an individual to stop ingesting food. Embodiments of this invention for regulating gut motility include methods and compositions comprising a trichothecene or other compound that stimulates a fed pattern of gut motility resulting in decreased food intake. Accordingly, this invention provides methods and compositions that may be used to regulate food intake and, thereby, to treat obesity in humans and other animals as well (see, e.g., the specification at p. 16, line 5-p. 19, line 13; p. 20, line 11-p. 22, line 21; Example 1, p. 31, line 23-p. 41, line 10; Example 4, p. 51, line 26-p. 58, line 5). Applicants' discovery was made possible by employing the relatively recent development of accurate, analytical methods for recording the components of gut motility (i.e., contractions and relaxations; simultaneously, if desired) and at multiple sites in gut tissues and organs (see, Krantis et al., *Can. J. Physiol. Pharmacol.*, 7: 894-903 (1996), of record).

With the discovery of compounds that regulate gut motility by acting through a particular neural pathway having a particular terminal neural receptor, i.e., the enteric P_{2X1} purinoceptor, Applicants have also described and claimed compositions and methods comprising non-trichothecene compounds that have the ability to regulate (i.e., stimulate or inhibit) gut motility and thereby regulate food intake. Such non-trichothecene compounds include ligands (such as ATP and analogs thereof) that bind directly to the terminal P_{2X1} receptors in the gut tissue to regulate (inhibit or stimulate) fed pattern of gut motility (see, e.g., p. 15, lines 18-p. 16, lines 2; p. 22, line 24-p. 25, line 7; p. 36, lines 7-23 in Example 1; Example 2, p. 41, line 13-p. 45, line 29; Example 3, p. 46, line 3-p. 51, line 23; Example 5, p. 58, line 8-p. 60, line 29, of the specification). Inhibition of fed pattern gut motility permits a "fasting" (or "grouped") pattern of gut motility that stimulates or prolongs food ***intake*** by an individual and thereby promotes weight gain (see, e.g., p. 3, lines 8-12; p. 13, line 27-p. 14, line 5; p. 14, line 21-p. 15, line 3; p. 15, line 31-p. 16, line 2, of the specification).

Accordingly, all of the claimed methods and compositions share the common technical feature of employing a compound that is able to regulate the pattern of gut motility associated with the food intake in a vertebrate animal. Accordingly, all of the pending claims of this application are united by an expressed contribution over the prior art in accordance with PCT Rule 13.2, which states:

> Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship ***among those inventions*** involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. (emphasis added)

Claims 1-39 comprise a compound that regulates the pattern of gut motility associated with food intake in vertebrate animals. Therefore, any art relevant to examination of one of the groups of claims will necessarily be the same art that is relevant to examination of the other group of claims. Since the claims share a special technical feature that enables the claims to be examined as a single group, no subdivision of the claims is necessary under PCT Rules 13.1 and 13.2.

Conclusion and Provisional Election Under 37 CFR 1.499

Applicants respectfully submit that in view of the foregoing remarks, the amendments, and added claims, it is clear that all of the claims (Claims 1-39) are related to a single inventive concept and have one or more common special technical features that are of the sort that are properly viewed as relating to a single general inventive concept to meet the requirement of unity of invention (PCT Rules 13.1 and 13.2). Applicants therefore respectfully request that the Examiner reconsider and withdraw the division of the claims into Groups I-VI.

Applicants believe that the division of the claims into Groups I-VI is improper and uncalled for, and do not in any way acquiesce in the reasons for the division set forth in the Office Action. Nevertheless, in order to be fully responsive to the Office Action, Applicants provisionally elect for examination the claims of Group I, i.e., Claims 1-7, which cover a method of treating obesity.

Additionally, in view of the above comments and the fact that a method of Claims 1-7 comprises use of a compound that ***must*** stimulate fed pattern gut motility in a vertebrate animal, then, at least, Claims 8-15 (method of stimulating fed pattern of gut motility), Claims 22-24 (method of identifying a compound for treating obesity that stimulates fed pattern of gut motility), Claims 25-31 (compounds and compositions that induce fed pattern of gut motility), and Claims 32-39 (method of regulating food intake using a compound that stimulates a fed pattern of gut motility) should also be counted as part of Group I. As amended, these claims all refer to the special technical feature of inducing a fed pattern of gut motility.

Respectfully submitted,

Thomas R. Berka

Thomas R. Berka, Ph.D., Reg. 39,606
Leon R. Yankwich, Reg. No. 30,237
YANKWICH & ASSOCIATES
201 Broadway
Cambridge, Massachusetts 02139
telephone: 617-374-3700
facsimile: 617-374-0055

Certificate of Express Mailing

The undersigned hereby certifies that this correspondence and accompanying documents are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, postage prepaid, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

Express Mail Label No.: EV 325775124 US

September 25, 2003
Date

Stephanie L. Leicht